

## Management of acute upper gastrointestinal bleeding

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# Management of acute upper gastrointestinal bleeding: an update for the general physician

K Siau<sup>1</sup>, W Chapman<sup>2</sup>, N Sharma<sup>3</sup>, D Tripathi<sup>4</sup>, T Iqbal<sup>5</sup>, N Bhala<sup>6</sup>

## Abstract

Acute upper gastrointestinal bleed (AUGIB) is one of the most common medical emergencies in the UK, with roughly one presentation every 6 min. Despite advances in therapeutics and endoscopy provision, mortality following AUGIB over the last two decades has remained high, with over 9,000 deaths annually in the UK; consequently, several national bodies have published UK-relevant guidelines. Despite this, the 2015 UK National Confidential Enquiry into Patient Outcome and Death in AUGIB highlighted variations in practice, raised concerns regarding suboptimal patient care and released a series of recommendations. This review paper incorporates the latest available evidence and UK-relevant guidelines to summarise the optimal pre-endoscopic, endoscopic, and post-endoscopic approach to and management of non-variceal and variceal AUGIB that will be of practical value to both general physicians and gastroenterologists.

**Keywords:** gastrointestinal bleed, haemorrhage, non-variceal, upper gastrointestinal bleeding, variceal

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## Introduction

Acute upper gastrointestinal bleed (AUGIB) is one of the most common medical emergencies in the UK, with an estimated incidence of 134 per 100,000,<sup>1</sup> roughly equating to one presentation every 6 min.<sup>2</sup> Despite advances in therapeutics and endoscopy provision, mortality following AUGIB over the last two decades has remained high, with over 9,000 deaths annually in the UK.<sup>3</sup>

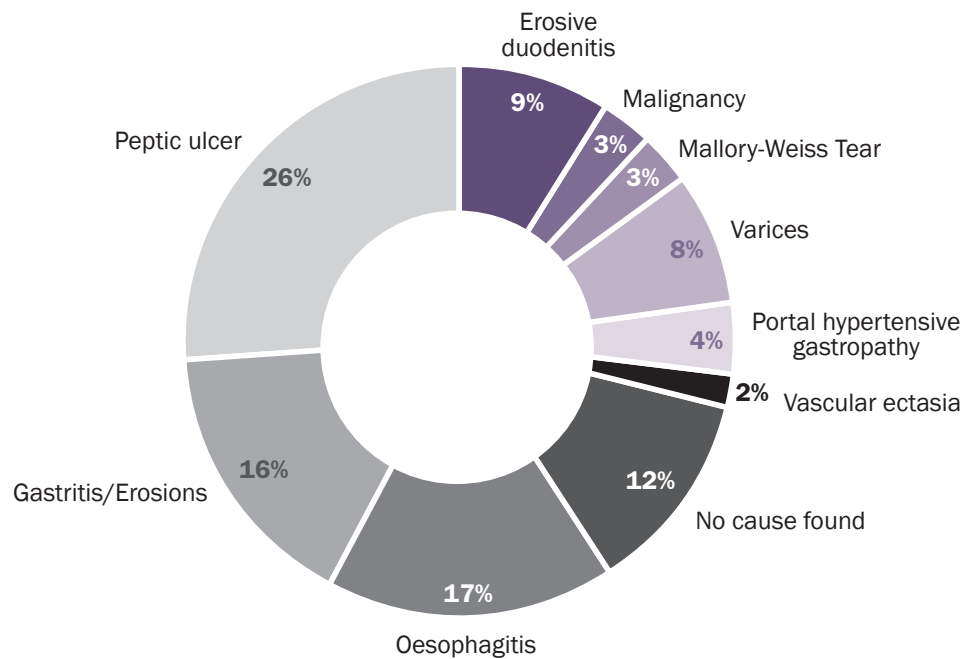
The first UK audit of AUGIB in 1993 reported an overall mortality of 14% (11% in patients admitted with AUGIB, and 33% of inpatients who develop AUGIB).<sup>4</sup> A follow-up national audit in 2007 demonstrated a mortality of 10% (7% in patients admitted with AUGIB, and 26% of inpatient bleeds).<sup>5</sup> Consequently, UK-relevant guidelines have been published by the National Institute for Health and Care Excellence (NICE),<sup>6</sup> the Scottish Intercollegiate Guidelines Network (SIGN) in conjunction with the British Society of Gastroenterology (BSG)<sup>7</sup> and, more recently, the European Society of Gastrointestinal Endoscopy (ESGE).<sup>8</sup> Despite this, the 2015 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) of UK patients with AUGIB highlighted variations in practice and raised concerns regarding suboptimal patient care, releasing a series of recommendations.<sup>2</sup>

## Diagnosis

Defined anatomically as bleeding in the upper gastrointestinal tract proximal to the ligament of Treitz,<sup>7</sup> AUGIB should be suspected in patients with haematemesis, coffee-ground vomiting, melaena or unexplained fall in haemoglobin. In up to 20% of cases, AUGIB may mimic lower gastrointestinal bleeding.<sup>9</sup> Features that predict AUGIB in cases of haematochezia include haemodynamic instability, increased serum urea:creatinine ratio, and reduced haematocrit.<sup>9</sup> The diagnosis is confirmed with endoscopy, which also serves to provide a therapeutic intervention. Based on endoscopic diagnoses from the 2007 audit,<sup>5</sup> the aetiologies of AUGIB are summarised in Figure 1.

Pragmatically, AUGIB can be divided into variceal and non-variceal UGIB (NVUGIB) causes, as there are important differences in management strategies. The proportion of variceal bleeding has doubled from 4% in the 1994 audit,<sup>4</sup> to 8% in 2007,<sup>5</sup> correlating with the increasing burden of liver disease. Peptic ulcer disease (PUD) remains the most common cause of AUGIB, despite reductions in PUD incidence and mortality over the last three decades.<sup>10</sup> These reductions are largely attributable to developments in proton pump inhibitors (PPI), endotherapy, *Helicobacter pylori* eradication, and reductions in use of non-steroidal anti-inflammatory drugs (NSAIDs).

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**Figure 1** Causes of acute upper GI bleeding in the UK<sup>5</sup>

## Pre-endoscopic management

### 1. Assessment and resuscitation

All patients with AUGIB should be promptly assessed and triaged for early fluid/blood product resuscitation and endoscopy.<sup>7</sup> In the unstable patient, early assistance from the intensive care team should be considered, especially in the case of airway compromise from haematemesis, hypoxia, or in cases of reduced level of consciousness from decompensated liver disease. The priority should be to ensure a safe airway, secure intravenous access for fluid resuscitation (at least two 16–18G intravenous cannulae), and pre-endoscopic optimisation.<sup>7</sup> Intraosseous access may be an early alternative to central venous cannulation if peripheral cannulation fails. Standard blood tests including clotting and a crossmatch should be urgently performed. Blood gas sampling may provide a rapid haemoglobin estimate and indicate acid-base disturbances and hyperlactataemia which may occur with tissue hypoperfusion. In the event of catastrophic haemorrhage, most hospitals in the UK have implemented switchboard-activated major haemorrhage protocols in line with national standards,<sup>11</sup> which expedites Group O-negative blood, platelets, and fresh frozen plasma, in addition to alerting key clinical and support personnel.<sup>11</sup> The duty endoscopist should be notified within 1 h of diagnosis,<sup>6</sup> and the patient placed nil by mouth.

Following resuscitation, a focused history and examination should ensue. This may determine an aetiology and/or complications related to AUGIB (Table 1). Features of peritonitis and bowel obstruction, which may indicate peptic ulcer perforation, are contraindications to endoscopy and warrant radiological and surgical assessment.

### 2. Risk Assessment

NICE and SIGN advocate a two-step risk assessment strategy.<sup>6,7</sup>

**Table 1** Pointers towards aetiology of UGIB based on history and examination findings

History/examination	Aetiology
NSAID use, previous ulcer, systemic illness	Peptic ulcer disease/gastroduodenitis
Alcohol excess, chronic liver disease, spider naevi, jaundice, hepatosplenomegaly, encephalopathy, ascites	Varices/portal hypertensive gastropathy
Excessive retching and vomiting prior to haematemesis	Mallory-Weiss tear
Weight loss, dysphagia	Stricture/malignancy
Chronic reflux, bisphosphonate use	Oesophagitis
Previous abdominal aortic aneurysm repair	Aorto-enteric fistula
Chronic kidney disease	Vascular ectasia
Recent endoscopic retrograde cholangiopancreatography	Post-sphincterotomy bleed
Peritonitis	Perforated ulcer
Cachexia/lymphadenopathy	Malignancy

#### Variceal assessment

This involves assessing the likelihood of varices prior to commencing variceal measures. The assessment is based on the presence of established varices, or risk factors for portal hypertension, such as established cirrhosis, stigmata of chronic liver disease, biochemical and radiological findings. Empirical management is discussed below.

#### Severity assessment

The Blatchford (Figure 2a) and Rockall scores (Figure 2b) are validated scoring systems that predict endoscopic and clinical outcomes,<sup>12,13</sup> and can be used as triaging tools for endoscopy. Patients with high risk scores should be

**Figure 2a** Blatchford Score<sup>13</sup>

Criteria (on admission)		Score
Hb - Male (g/L)	Hb - Female (g/L)	
120-130	100-120	1
100-120		3
<100	<100	6
Urea (mmol/L)		
6.5-8		2
8-10		3
10-25		4
≥25		6
Systolic blood pressure (mmHg)		
100-109		1
90-99		2
<90		3
Others		
Pulse ≥100		1
Melaena		1
Syncope		2
Hepatic disease		2
Cardiac failure		2

**Table 2** NICE guidelines for correction of coagulopathy during AUGIB<sup>6</sup>

Coagulopathy	Threshold	Management
<b>Platelets</b>	<50 x10 <sup>9</sup> /L	Platelet transfusion
<b>INR</b>	>1.5	FFP PCC (if on warfarin)
<b>aPTT</b>	>1.5	FFP
<b>Fibrinogen</b>	<1.5g/L	FFP Cryoprecipitate (if low despite FFP)

INR, International Normalised Ratio; aPTT, activated partial thromboplastin time ratio; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma.

prioritised for endoscopy, with all cases performed within 24 h of admission. Low-risk patients, i.e. Blatchford score of 0–1, may be considered for discharge with outpatient endoscopy.<sup>8,14</sup> Recently, the AIMS65 score has been introduced as another pre-endoscopic risk assessment tool, comprising **A**lbumin (< 3 g/L), **I**NR > 1.5, **M**ental state alteration, **S**ystolic blood pressure < 90, **A**ge > 65.<sup>15</sup> Although AIMS65 has not been adopted in UK guidelines, it is practical and appears superior to pre-endoscopic Rockall and Blatchford scores in predicting

**Figure 2b** Rockall score.<sup>12</sup> \*Denotes components of pre-endoscopic Rockall Score

Criteria (on admission)	Score
Age*	
<60	0
60-79	1
≥80	2
Shock*	
Pulse >100	1
Systolic BP <100mmHg	2
Co-morbidity*	
Cardiac, other major	2
Renal/liver failure, cancer	3
Endoscopic Diagnosis	
Normal, Mallory-Weiss	0
Ulcer, erosion, oesophagitis	1
Cancer	2
Endoscopic SRH	
Clean base ulcer, flat pigmented spot	0
Active bleeding, clot, vessel, blood	2

inpatient mortality, length of stay, and need for intensive care admission.<sup>16</sup>

### 3. Pre-endoscopic medical management

Following risk assessment, patients should be referred for endoscopy once medically optimised. It is worth emphasising that endoscopy is routinely performed with oxygen delivered via nasal cannulae. Patients who remain hypoxic despite this may benefit from anaesthetic input for airway intubation if endoscopy is urgently indicated. Furthermore, the following aspects should be considered:

#### Coagulopathy

Coagulopathy should be identified and corrected prior to endoscopy (Table 2). ESGE recommends the INR be corrected to < 2.5 prior to performing endoscopy.<sup>8</sup> Patients with AUGIB while on novel oral anticoagulants, should be discussed with local haematologists; there are no data to support routine administration of fresh frozen plasma.

#### Proton pump inhibitors (PPI)

The guidance on whether to administer PPI therapy prior to endoscopy is conflicting. A 2010 Cochrane meta-analysis of six randomised controlled trials (RCTs) (n = 2223) showed that PPIs before endoscopy significantly reduced stigmata of recent haemorrhage at index endoscopy (37.2% vs 46.5%; OR 0.67, 95% CI 0.54–0.84) and the need for endotherapy (8.6% vs 11.7%; OR 0.68, 95% CI 0.50–0.93), without affecting rates of rebleeding, surgery, or mortality.<sup>17</sup> As this approach may mask targets for therapy, NICE and BSG do not recommend routine PPI administration.<sup>6,7</sup> However,

following cost-effectiveness analyses, ESGE recommends pre-endoscopic PPI infusion.<sup>8</sup>

#### *Variceal measures (terlipressin and antibiotics)*

Patients with suspected variceal haemorrhage should be considered for prompt administration of variceal measures, terlipressin (or an alternative) and antibiotics.<sup>18</sup> Terlipressin, a vasopressin analogue, increases systemic vascular resistance, reduces cardiac output, and reduces portal pressures by approximately 20%.<sup>19</sup> The dose in variceal haemorrhage is 2 mg four times a day. A meta-analysis of seven RCTs (n = 443) showed an overall efficacy of achieving haemostasis with terlipressin in 75–80%, and significant reductions in mortality of 34% (95% CI 12%–51%).<sup>20</sup> Trials comparing terlipressin to somatostatin have shown no differences in mortality or rebleeding.<sup>19,21</sup> Physicians should be aware of contraindications to terlipressin which include arterial disease, hyponatraemia, myocardial ischaemia, severe cardiac failure and prolonged QTc interval. Somatostatin or octreotide may be considered for patients with contraindications.<sup>18,21</sup>

Bacterial infections are common in cirrhotic patients with AUGIB. Twenty percent of patients have infections within 48 h, increasing to 36% after 7 days.<sup>22</sup> Infection is associated with significantly increased rebleeding risk (43.5% vs 9.8%) and mortality (47.8% vs 14.6%).<sup>22</sup> It remains unclear whether bleeding or infection constitutes the primary event. A meta-analysis of 12 RCTs associated Gram-negative antibiotic prophylaxis with reduced mortality (RR 0.79, 95% CI 0.63–0.98) and rebleeding (RR 0.53, 95% CI 0.38–0.74).<sup>23</sup> As such, antibiotic prophylaxis has been adopted as a standard of care in cirrhotic patients with AUGIB.<sup>6,7,8,18</sup>

#### *Prokinetics*

A frequent question relates to pre-endoscopic prokinetic use in AUGIB. A meta-analysis of eight studies (n = 598) on the use of erythromycin infusion prior to endoscopy in AUGIB found significant improvements in adequate mucosal visualisation (OR 4.1, 95% CI 2.0–8.5), reductions in the need for second-look endoscopy (15.1% vs 25.7%, OR 0.51; 95% CI: 0.34–0.77) and length of stay (mean difference -1.75; 95% CI: -2.43 to -1.06).<sup>24</sup> ESGE recommends a 250 mg erythromycin infusion 30–120 min pre-endoscopy in patients with clinically severe/ongoing AUGIB.<sup>8</sup> There is no evidence to support the use of metoclopramide.

#### *Tranexamic acid*

The role of tranexamic acid in AUGIB is unclear and has not been recommended in guidelines. A Cochrane meta-analysis showed a reduction in mortality (RR 0.61, 95% CI: 0.42–0.89),<sup>25</sup> but the authors considered the studies to be insufficiently powered and of poor quality, with loss of benefit after adjusting for bias. Currently, the HALT-IT trial is open for recruitment and aims to clarify the efficacy of tranexamic acid.<sup>26</sup> HALT-IT is a pragmatic, double-blind, placebo-controlled trial comparing 24 h tranexamic acid infusion with placebo, aiming to recruit 8,000 patients by November 2017.<sup>26</sup> Clinicians should consider liaising

with their clinical research departments to facilitate trial recruitment at the point of presentation.

## Endoscopic management

Endoscopy should be carried out within 24 h of presentation.<sup>2,6</sup> Endoscopy at an early stage enables the determination of the cause of bleeding, prognosis and therapeutic interventions to stop bleeding. The management of bleeding lesions varies according to whether it is from a variceal or non-variceal source.

### 1. NVUGIB

A peptic ulcer may present with high risk stigmata. These are: (i) active bleeding, (ii) a non-bleeding visible vessel, (iii) adherent clot. Endoscopic haemostasis of such lesions has been shown to reduce mortality, rebleeding risk and the need for surgery.<sup>7,27,28</sup> Endoscopic therapies for NVUGIB comprise injection therapy, thermal treatments, mechanical adjuncts and spray therapy.

#### *Injection therapy*

Injection of adrenaline into and around the point of bleeding will reduce the rate of rebleeding.<sup>29</sup> However, it is recommended that adrenaline injection is accompanied by another method of haemostasis.<sup>6,7,27</sup> A meta-analysis of 16 studies comparing adrenaline monotherapy with dual therapy (adrenaline with an additional haemostatic technique) showed that dual therapy was superior in reducing rebleeding (10.6% vs 18.4%, OR 0.53, 95% CI 0.40–0.69), emergency surgery (7.6% vs 11.3%, OR 0.64, 95% CI 0.46–0.90), and mortality (2.6% vs 5.1%, OR 0.51, 95% CI 0.31–0.84).<sup>30</sup>

#### *Thermal treatment*

There are two types of thermal haemostasis in endoscopy: contact and non-contact. Contact treatments involve applying pressure and heat via a heater probe using monopolar diathermy; the aim of this is to compress and seal a bleeding lesion. The probe is applied until the treated areas are black and depressed.<sup>7</sup> Non-contact thermal haemostasis includes argon plasma coagulation, which is sufficient for the treatment for superficial angiodysplastic lesions.<sup>31</sup>

#### *Mechanical treatment*

The most common mechanical haemostasis device is the endoclip or haemoclip. These are stainless steel clips which are passed through the endoscope and deployed to the bleeding lesion. When applied correctly, clips provide mechanical compression to the bleeding vessel, resulting in haemostasis. In a meta-analysis,<sup>32</sup> clip application was shown to be superior to injection therapy in achieving definitive haemostasis (86.5% vs 75.4%, RR 1.14, 95% CI: 1.00–1.30), but comparable to thermal treatment. Clip deployment has the additional advantage of identifying the bleeding lesion at interventional radiology (see below).

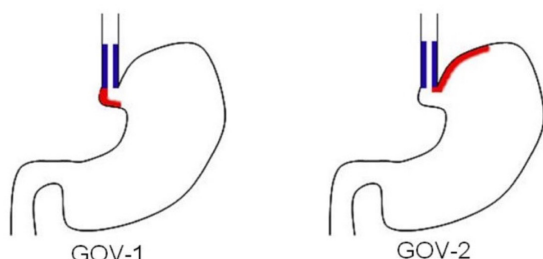
#### *Haemostatic agents*

Recently, topical haemostatic agents such as Hemospray

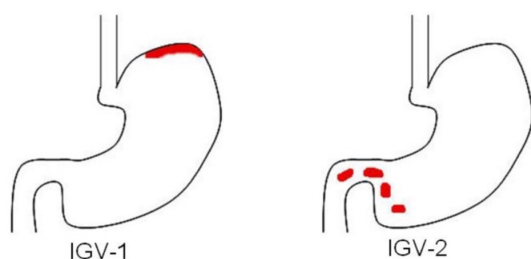


**Figure 3** Classification of gastric varices.<sup>35</sup> GOV-1: oesophageal varices extending along lesser curve; GOV-2: oesophageal varices extending along fundus; IGV-1: Isolated fundal varices; IGV-2: Isolated varices in gastric antrum, body or pylorus

### Gastro-oesophageal varices (GOV)



### Isolated gastric varices (IGV)



(Cook Medical) have been released. These agents achieve haemostasis by mechanically adhering to a bleeding site, resulting in mechanical tamponade, and by activating coagulation factors to promote thrombus formation. Hemospray is safe, as the powder is not absorbed systemically. Hemospray is sprayed via an endoscopically-directed catheter, and has the ability to cover large areas with multiple bleeding points, without the need for precise lesion targeting. It is a suitable choice for bleeding lesions such as haemorrhagic gastritis, portal hypertensive gastropathy, gastric antral vascular ectasia, radiation-induced mucosal injury and malignancy-related bleeding.<sup>33</sup> As such, Hemospray has emerged as a promising alternative treatment for difficult to access bleeding lesions or as an adjunct to combinations of injection therapy with thermal or mechanical treatments.<sup>34</sup>

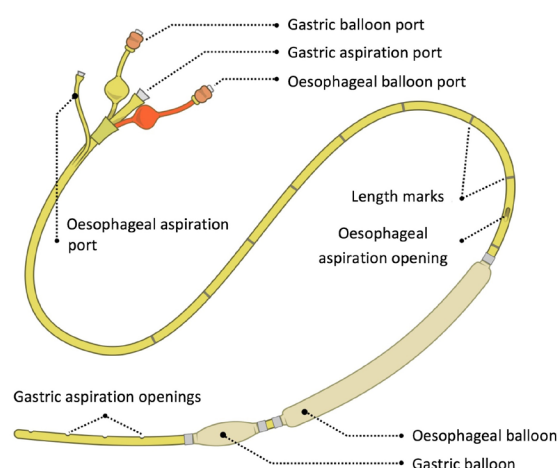
## 2. Variceal

Varices occur as a result of portal hypertension, which leads to increases in portal pressure and development of portosystemic shunts. In the upper gastrointestinal tract, these occur through the gastro-oesophageal veins, leading to varices in the distal oesophagus and upper stomach. Endoscopic options for variceal bleeding include band ligation, sclerotherapy and Sengstaken tube insertion. Management of gastric varices depend on the anatomical subtype (Figure 3).<sup>18,35</sup> The evidence base for endoscopic management of gastric varices is much weaker than for oesophageal varices.

#### Variceal band ligation (VBL)

Although sclerotherapy had historically been the mainstay of

**Figure 4** Sengstaken-Blakemore tube



treatment for bleeding varices,<sup>36</sup> this has been superseded by VBL for oesophageal varices. A meta-analysis of seven randomised trials found VBL to be superior to sclerotherapy in reducing rebleeding (OR 0.52, 95% CI 0.37–0.74) and mortality (OR 0.67, 95% CI 0.46–0.98).<sup>37</sup> VBL should be used in conjunction with terlipressin, somatostatin or octreotide.<sup>18</sup> VBL involves attaching a small plastic tube to the end of the endoscope, around which small rubber bands are placed. The endoscope is used to suck the varix into the tube and a rubber band is deployed to induce strangulation and thrombosis of the varix. VBL is also recommended by the BSG for the management of type 1 gastro-oesophageal varices (GOV-1), which occur in 75% of gastric varices. The most common complication of VBL is post-band ulceration, the size of which may be reduced by PPI use.<sup>38</sup>

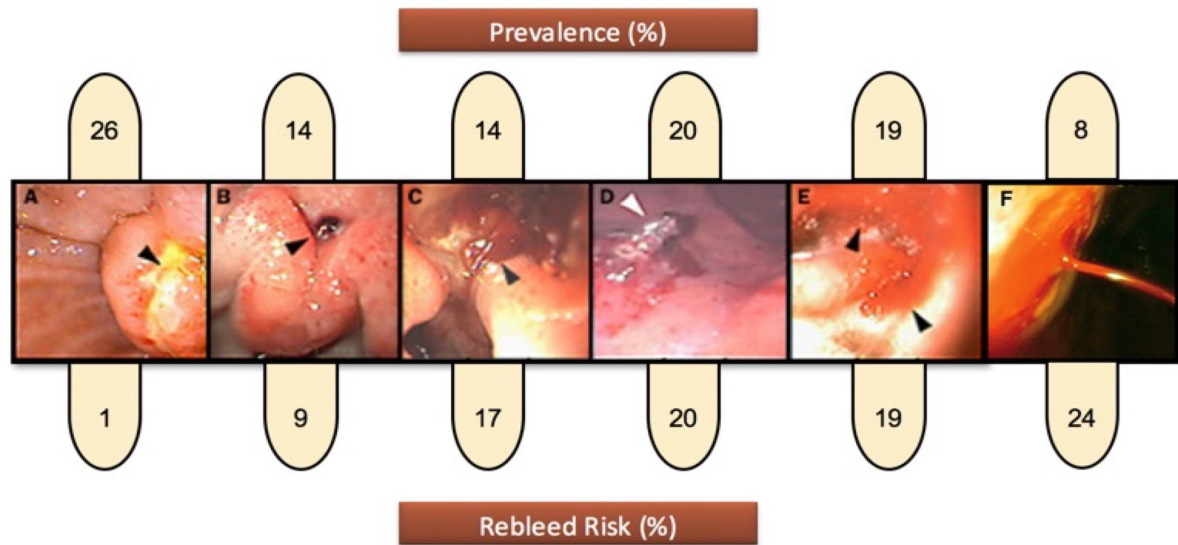
#### Cyanoacrylate and thrombin

Cyanoacrylate, also known as 'glue', is a strong adhesive with multiple industrial and domestic applications. For type 2 gastro-oesophageal varices (GOV-2) and isolated gastric varices (IGV), cyanoacrylate has been shown to be superior to VBL in achieving haemostasis and reducing rebleeding,<sup>39,40</sup> and has been approved by NICE and BSG.<sup>6</sup> Recently, thrombin injection has been accepted as an alternative to cyanoacrylate for gastric varices,<sup>18</sup> with haemostasis rates of 94% and rebleeding rates of 18%.<sup>41</sup> There have been no head-to-head trials comparing thrombin to sclerosant therapy.

#### Balloon tamponade

Balloon tamponade is indicated in failure of haemostasis with bleeding oesophageal varices and most types of gastric varices (GOV-1, GOV-2, and IGV-1).<sup>18</sup> The Sengstaken-Blakemore tube (SBT) (Figure 4) is the most common device for balloon tamponade. It achieves haemostasis in 91.5% of cases, with recurrence of bleeding in approximately 50% of cases after balloon deflation.<sup>42</sup> It is thus useful as a bridge to a more definitive procedure (discussed below). Complications of SBT occur in 15–20% of patients, and include pressure necrosis, misplacement, aspiration pneumonia and oesophageal rupture.<sup>18</sup> Due to its poor tolerability, patients often require heavy sedation and intubation prior to SBT

**Figure 5** Forrest classification of PUD with prevalences and post-endothecopy rebleed risks based on data from Guglielmi et al.<sup>49</sup>  
 A) Forrest 3: Clean base, B) Forrest 2c: Flat pigmented spot, C) Forrest 2b: Adherent clot, D) Forrest 2a: Visible vessel, E) Forrest 1b: Oozing vessel, F) Forrest 1a: Spurting vessel



insertion and hence should be managed in an intensive care unit.

#### Oesophageal stenting

Lately, there have been data supporting the role of self-expanding metal stent placement in cases of refractory bleeding oesophageal varices.<sup>43</sup> Self-expanding metal stents have been shown to be superior to SBT in this setting, with a recent RCT showing improved treatment success, defined as survival at day 15 with control of bleeding and without serious adverse events (66% vs 20%,  $p = 0.025$ ).<sup>44</sup> Self-expanding metal stents can be deployed without radiological guidance and can be left in for 14 days (vs 2 days for SBT),<sup>18</sup> and have been approved by NICE.<sup>45</sup>

### 3. Endoscopic Reporting

A good endoscopy report is vital for recording and handover purposes. Although quality assurance for diagnostic gastroscopy has been outlined,<sup>46</sup> quality assurance on endoscopy reporting specific to AUGIB has not featured in national guidelines. A major recommendation from the 2015 NCEPOD report was for all patients to have a clearly documented rebleed plan.<sup>2</sup> In 2016, the Joint Advisory Group for Gastrointestinal Endoscopy (JAG) implemented AUGIB DOPS (Directly Observed Procedural Skills) forms to include assessment of endoscopy reporting by endoscopy trainees. This included documentation of the following aspects: indications, pre-procedural risk scoring, accurate description of identified lesion and location, photodocumentation, description of rebleeding stigmata and endotherapy, complications/difficulties encountered, rebleeding risk, specific treatments to be initiated, and rebleeding plan.<sup>47</sup> The report should also include instructions on re-initiation of feeding and antithrombotic drugs.<sup>48</sup>

### Post-endoscopic management

Following endoscopy, physicians should carefully scrutinise the endoscopy report. High risk patients should be escalated to a high dependency unit setting. Patients should be monitored for rebleeding and medical comorbidity. Rebleeding risk should be quantified according to factors outlined on the report, such as: adequacy of haemostasis, interventions applied (monotherapy vs combination therapy), complete Rockall score,<sup>12</sup> and Forrest classification of PUD (Figure 5). A discussion with the endoscopist should take place if there is a lack of clarity. The following evidence-based management should be considered depending on the endoscopic findings:

#### 1. NVUGIB

##### PPI therapy

Increased gastric pH has been linked with improved clot stability.<sup>50</sup> A landmark placebo-controlled randomised trial from Hong Kong showed that continuous omeprazole infusion (80 mg intravenous bolus followed by 8 mg/h for 72 h) after endotherapy for peptic ulcer was superior to placebo in reducing recurrent bleeding, transfusion requirements and hospital stay.<sup>51</sup> This has since been replicated in a Cochrane review,<sup>52</sup> and unanimously incorporated into guidelines for post-endoscopic management of peptic ulcer bleeding.<sup>6-8</sup>

Moreover, the efficacy of PPI may not be restricted to PUD. A meta-analysis of 26 trials ( $n = 4670$ ) comparing PPI to placebo after any high-risk non-variceal lesion showed reduced rebleeding (OR 0.48; 95% CI 0.40–0.57) and surgery (OR 0.61; 95% CI 0.48–0.76) in favour of PPI, but not overall mortality.<sup>53</sup> More recently, the method of PPI administration has been challenged, with meta-analysis data showing non-inferiority in rebleeding risk with intermittent vs continuous regimens (RR 0.72,  $p = 0.10$ ), or with oral versus intravenous formulations (RR 0.92,  $p = 0.95$ ).<sup>54</sup> NICE recommends routine administration of PPI to patients with NVUGIB and stigmata

of recent haemorrhage shown at endoscopy,<sup>6</sup> but does not specify the route, dosage or duration. ESGE recommends for patients with peptic ulcers with flat pigmented spot (Forrest IIc) or clean base (Forrest III) to be discharged with once daily oral PPI.<sup>8</sup>

#### *Helicobacter pylori*

*H. pylori* is perhaps the single most important aetiological factor in PUD. Although the prevalence of *H. pylori* appears to have fallen since the 1990s,<sup>55</sup> infection rates in bleeding PUD remain high.<sup>56</sup> A 2012 study found a prevalence of 66% in uncomplicated duodenal ulcers and 47% of gastric ulcers, with an overall prevalence of 66% in bleeding PUD,<sup>56</sup> which was similar to previous estimates of 71% in bleeding duodenal ulcers and 65% in bleeding gastric ulcers.<sup>57</sup> However, the true prevalence in bleeding PUD may be higher;<sup>55</sup> it is widely acknowledged that sensitivity of diagnostic tests for *H. pylori* is diminished during AUGIB, with false negative rates estimated to be between 25 and 50%.<sup>58</sup>

Detection and eradication are important as they lead to improved outcomes, and obviate the need for long term PPI.<sup>59</sup> In a Cochrane meta-analysis of patients with *H. pylori*-related bleeding PUD (without NSAID use), *H. pylori* eradication was superior to non-eradication (OR 0.16, 95% CI 0.09–0.30,  $p < 0.00001$ , NNT = 7) or long-term antisecretory therapy (OR 0.14, 95% CI 0.05–0.43;  $p = 0.0006$ , NNT = 20) for preventing rebleeding.<sup>59</sup> Subsequently, AUGIB guidelines have called for *H. pylori* assessment (ideally during endoscopy with biopsy methods, urea breath testing or monoclonal stool antigen testing).<sup>6–8</sup> If positive, *H. pylori* eradication should be commenced at reintroduction of oral feeding,<sup>60</sup> as delayed treatment can lead to loss of follow-up and poorer compliance. Currently, NICE recommends a 7-day twice daily regimen consisting of PPI and dual antibiotic therapy (amoxicillin and clarithromycin/metronidazole) for eradication,<sup>61</sup> although evidence exists to support extending the duration to 14 days,<sup>62</sup> and for first-line sequential therapy.<sup>63</sup> PPI treatment should continue for a total of 4 weeks,<sup>7</sup> and discontinued for at least 2 weeks before *H. pylori* reassessment.<sup>7</sup> Although NICE advocates urease breath testing for reassessment,<sup>61</sup> stool antigen testing 6 weeks after discharge appears to be a reasonable alternative.<sup>60</sup> Second-line measures should be started for eradication failure.<sup>61</sup>

#### *Transfusions thresholds*

Two well-designed RCTs have compared outcomes between restrictive and liberal transfusion strategies in haemodynamically stable patients with AUGIB.<sup>64,65</sup> Villanueva et al. demonstrated that a transfusion trigger of 70 g/L vs 90 g/L haemoglobin was associated with significantly reduced 6-week mortality (HR 0.55, 95% CI 0.33–0.92), rebleeding (HR 0.62, 95% CI 0.43–0.91), adverse events (HR 0.73, 95% CI: 0.56–0.95) and blood transfusions, without a significant difference in 6 week haemoglobin.<sup>64</sup> Moreover, the authors correlated a liberal approach with increases in portal pressures,<sup>64</sup> which is implicated in variceal bleeding. The TRIGGER trial,<sup>65</sup> which was a UK-based pragmatic RCT ( $n = 936$ ), showed no significant difference in outcomes between

the restrictive (80 g/L) and liberal (100 g/L) strategies. Based on this, ESGE recommends a restrictive transfusion strategy (target haemoglobin between 70–90g/L) after haemostasis.<sup>8</sup>

#### *Iron replacement*

Patients are often discharged from hospital with anaemia after AUGIB.<sup>66</sup> One retrospective study reported a prevalence of 80%, with iron supplementation in only 16%.<sup>66</sup> Adoption of restrictive transfusion strategies may increase rates of anaemia at discharge. One RCT ( $n = 97$ ) assigned patients with post-AUGIB anaemia to either placebo, oral iron (200 mg daily for 3 months) or intravenous iron (a single 1000 mg infusion).<sup>67</sup> Iron replacement was superior to placebo in reducing rates of anaemia at 13 weeks (17% vs 70%,  $p < 0.01$ ), with highest efficacy in the intravenous group.<sup>67</sup> Although iron supplementation is not prescribed in AUGIB guidelines this should nonetheless be considered prior to discharge.

#### *Antithrombotic therapy*

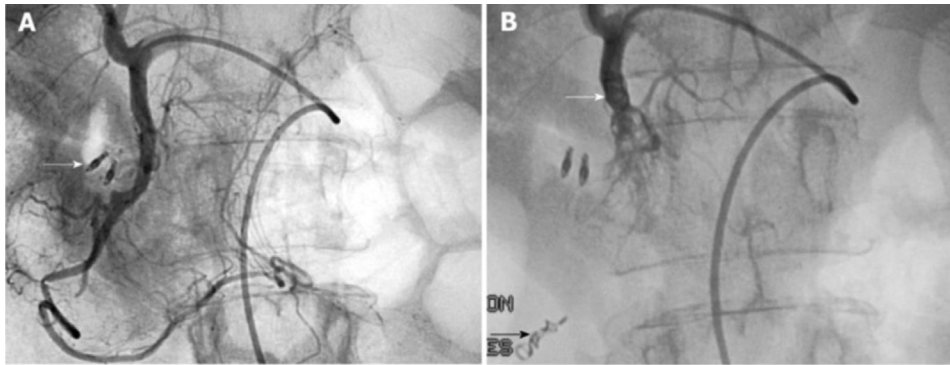
Antithrombotic drugs, e.g. aspirin, thienopyridines and anticoagulants, are often stopped during AUGIB and not resumed.<sup>68</sup> These are often indicated for secondary prophylaxis of cardiovascular and thrombotic events. In an RCT ( $n = 156$ ) involving patients with NVUGIB on aspirin, discontinuation of aspirin was associated with increased all-cause mortality at 8 weeks compared to aspirin maintenance (10.3% vs 1.3%,  $p = 0.001$ ).<sup>69</sup> Mortality mainly arose due to thrombotic events, without a significant difference in rebleeding rates.<sup>69</sup> This effect does not appear to be limited to aspirin; one study has associated discontinuation of any antithrombotic therapy following AUGIB with increased cardiovascular mortality (RR 4.5,  $p = 0.03$ ), all-cause mortality (RR 3.0,  $p = 0.003$ ), and cardiovascular events (RR 6.1,  $p = 0.003$ ) over one year of follow-up.<sup>68</sup>

NICE recommends continuing low-dose aspirin for secondary prevention of vascular events in patients with AUGIB after haemostasis.<sup>6</sup> ESGE recommends immediate resumption of aspirin following index endoscopy if the risk of rebleeding is low (e.g. Forrest IIc and Forrest III lesions).<sup>8</sup> In patients with high risk peptic ulcer (Forrest 1a to Forrest 2b lesions), ESGE recommends early reintroduction of aspirin by day 3 after endotherapy.<sup>8</sup> For thienopyridines/anticoagulants, indications should be reviewed, with specialist input if necessary, and resumed if there are compelling indications to reduce cardiovascular risk.<sup>6</sup>

#### *Rebleeding (non-variceal)*

Rebleeding occurs in approximately 13–23% of cases.<sup>2,5</sup> NICE recommends offering repeat endoscopy to patients who rebleed, or if there is doubt regarding adequate haemostasis at index endoscopy.<sup>6</sup> If there is a failure of endoscopic haemostasis, unstable patients should be considered for interventional radiology or surgery. In the 12% of patients where there is no cause apparent on index endoscopy,<sup>5</sup> repeat oesophagogastroduodenoscopy should be considered in the event of rebleeding,<sup>6</sup> with a view to colonic and small bowel investigations if haemorrhage persists.





**Figure 6** Arterial embolisation in a patient with rebleeding from a duodenal ulcer at endoscopy despite injection and clip therapy.<sup>74</sup>

A: Angiography, guided by clip position (arrow), without active extravasation; B: Result after coil embolisation of the distal and proximal gastroduodenal artery

#### CT angiography and transcatheter arterial embolisation

CT angiography is a non-invasive assessment tool for obscure gastrointestinal bleeding, with a sensitivity of 86% and specificity of 95%.<sup>70</sup> It can also detect vascular malformations, neoplasms, small bowel and lower gastrointestinal bleeding sources, in addition to providing evidence of stigmata of recent haemorrhage, such as extravasated blood in the bowel lumen. However, CT angiography requires the rate of haemorrhage to be at least 0.5 ml/min to reliably demonstrate luminal extravasation of contrast at the bleeding source.<sup>71</sup> If confirmed, the patient may proceed to catheter angiography (Figure 6). This is performed by interventional radiologists, who obtain access via the femoral artery and perform selective catheterisation of mesenteric vessels to prepare for transcatheter arterial embolisation (TAE). The coeliac artery and its gastric and gastroduodenal branches are often interrogated first, as most peptic ulcers receive blood supply from the gastroduodenal artery.<sup>72</sup> In the absence of a bleeding source, the superior and inferior mesenteric arteries may be evaluated. If a bleeding source is identified, TAE is performed.<sup>72</sup> Although metal coils are the embolic agent of choice, additional options include glue, polyvinyl alcohol particles, and Gelfoam (absorbable compressed sponge).<sup>72</sup> Potential complications of TAE include transient abdominal pain, bowel ischaemia, arterial injury and contrast nephropathy.<sup>72</sup>

Although salvage surgery has been traditionally the default option for patients with uncontrolled haemorrhage, the 2007 UK audit showed higher mortality after surgery than TAE (29% vs 10%).<sup>73</sup> The audit showed that patients who rebled were more likely to undergo surgery (2.2%) than TAE (1.5%), with surgical modalities consisting of: ulcer under-run (69%), ulcer excision (3%), ulcer excision with vagotomy/pyloroplasty (2%), partial gastrectomy (9%), and other (16%). At the time, less than 10% of hospitals had access to 24 h interventional radiology. No prospective studies or RCTs have compared surgery to TAE. From the 2015 NCEPOD audit,<sup>2</sup> only 27% of hospitals could offer 24 h on-site embolisation. Unfortunately, the choice of therapy will remain dictated by service availability.

#### Follow-up

Most patients do not receive outpatient follow-up after NVUGIB. Follow-up endoscopy for gastric ulcers after 6–8 weeks is recommended,<sup>61</sup> depending on the size of the lesion, as gastric ulcers may harbour malignant change. Colonoscopic or small bowel assessment may be warranted

in recurrent or occult bleeding. It is reasonable to arrange community follow-up monitoring of symptoms, biochemistry, and review of medications.

## 2. Variceal

#### Terlipressin

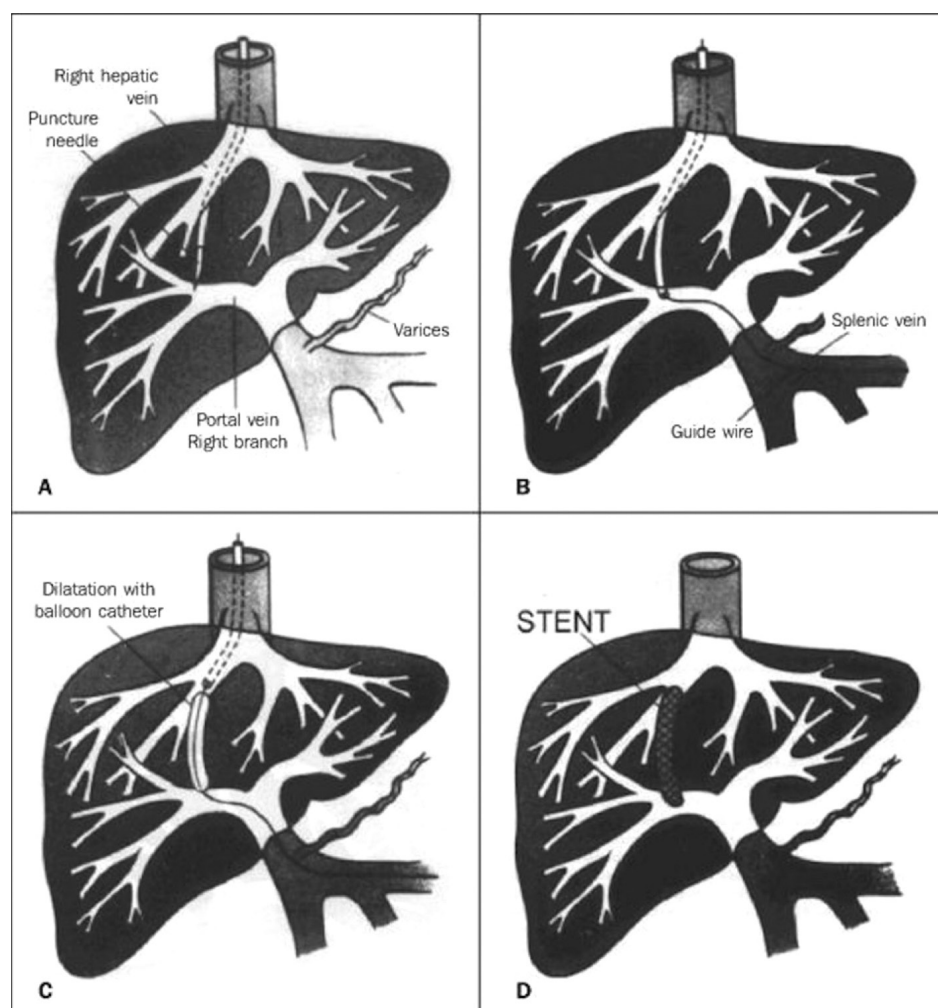
The pre-endoscopic role of terlipressin has been discussed above. The optimal duration of terlipressin has only been assessed in one trial,<sup>75</sup> in which 509 patients with variceal haemorrhage who had been stabilised with sclerotherapy and 48 h of terlipressin were randomised to an additional 5 days of terlipressin or placebo, before repeating sclerotherapy at day 7. Maintenance of terlipressin was associated with reduced 28-day rebleeding rates (9.7% vs 21.8%,  $p = 0.001$ ), but without differences in mortality. Although terlipressin has a 72 h manufacturer's licence, NICE recommends continuing until certainty of haemostasis or after 5 days, unless other indications exist for its use, such as hepatorenal syndrome.<sup>6</sup>

#### Non-selective beta blockers

After the first variceal haemorrhage, the risk of rebleeding is 15–30% within the subsequent 6 weeks.<sup>76</sup> Currently, the mainstay of pharmacological secondary prophylaxis is with non-selective beta-blockers, such as propranolol or carvedilol.<sup>18</sup> Propranolol reduces portal pressures through splanchnic vasoconstriction and reduced cardiac output. A meta-analysis of 12 RCTs (11 with propranolol) for secondary prophylaxis of variceal bleeding showed that, over two years, use of non-selective beta-blockers was associated with freedom from variceal rebleeding (20% mean difference, 95% CI: 11–28%,  $p < 0.001$ ), and increased survival (5.4% mean difference, 95% CI: 0%–11%,  $p < 0.05$ , RR 1.27).<sup>77</sup> Carvedilol, which has vasodilator properties due to  $\alpha_1$ -receptor blockade, has been shown in haemodynamic studies to reduce portal pressures more effectively than propranolol.<sup>78</sup> However, there has been no randomised trial comparing carvedilol with carvedilol + VBL. As such, recent BSG guidelines recommend use of propranolol or nadolol for secondary prevention of variceal bleeding, with carvedilol as an alternative.<sup>18</sup> The addition of isosorbide mononitrate to non-selective beta-blockers does not appear to affect rebleeding or mortality,<sup>79</sup> and has not been recommended in guidelines.

#### Variceal band ligation (VBL)

Patients should be scheduled for elective repeat endoscopy 2–4 weeks after variceal haemorrhage until eradication of varices,<sup>18</sup> although this is controversial.<sup>80</sup> One RCT of monthly

**Figure 7** TIPSS procedure.<sup>84</sup>

A: Insertion of a catheter-guided needle passed from the internal jugular to right hepatic vein to puncture the portal vein. B: Insertion of guide-wire into the portal system. C: Dilatation of hepatic parenchyma between the portal vein and hepatic vein. D: Stent placement in the newly formed tract

vs biweekly VBL found an increased risk of post-VBL ulcers in the biweekly group (57% vs 11%,  $p < 0.001$ ) without significant differences in mortality.<sup>81</sup> After successful eradication of varices, patients should be booked for endoscopy at 3 months, then 6-monthly thereafter.<sup>18</sup> Recurrent varices should be treated with VBL until eradication.

#### Transfusion thresholds

The rationale for a restrictive transfusion strategy in variceal bleeding has been covered in the NVUGIB section. BSG recommends a transfusion threshold of 70–80 g/L in haemodynamically stable patients with variceal haemorrhage.<sup>18</sup>

#### Transjugular intrahepatic portosystemic shunt (TIPSS) and rebleeding

Patients who rebleed should be considered for urgent repeat endoscopy and VBL. If rebleeding is difficult to control, SBT or self-expanding metal stent can be attempted until salvage TIPSS or surgical shunt surgery is performed.<sup>18</sup> The aim of TIPSS is to rapidly reduce portal pressures by creating a portosystemic shunt across the liver parenchyma (Figure 7). TIPSS is performed by specialist interventional radiologists, and has been shown to be superior to VBL for preventing rebleeding (19.0% vs 43.8%, OR 0.32, 95% CI 0.24–0.43,  $p < 0.00001$ ), but with increased rate of post-procedural encephalopathy (OR 2.21, 95% CI 1.61–3.03,  $p < 0.00001$ ).<sup>82</sup>

**Table 3** Contraindications to TIPSS<sup>83</sup>

Absolute	Relative
Primary prevention	Hepatic encephalopathy
Severe pulmonary hypertension (pulmonary arterial pressure >45mmHg)	Hepatoma
Polycystic liver disease	Hepatic vein/portal vein thrombosis
Uncontrolled systemic infection	Severe uncorrectable coagulopathy
Unrelieved biliary obstruction	Moderate pulmonary hypertension
Severe congestive cardiac failure	Advanced cirrhosis (Child C)

Contraindications to TIPSS are summarised in Table 3.<sup>83</sup> For those with anatomical contraindications, shunt surgery may be considered.

The role of TIPSS may not be confined to salvage treatment. There is RCT evidence,<sup>85</sup> recently endorsed by BSG,<sup>18</sup> to support the role for early TIPSS in select patients (Child B and Child C cirrhosis with score < 14) within 72 h of a variceal bleed. As such, referral to a specialist liver unit for TIPSS may be appropriate even after index presentation with variceal

**Table 4** Key findings and recommendations from NCEPOD 2015<sup>2</sup>

NCEPOD Findings	NCEPOD Recommendation
23% of patients suffered a rebleed.	Care pathways for all GI bleeds should include, as a minimum, risk assessment, escalation of care, transfusion documentation, core procedural documentation, network arrangements and rebleed plans. The pathway needs to be clearly documented.
42% who had an endoscopy for NVUGIB and 32% for variceal bleed had no rebleed plan.	All patients with a GI bleed must have a clearly documented rebleed plan agreed at the time of each diagnostic or therapeutic intervention.
24% died overall whilst 38% died who developed a GI bleed whilst already in hospital.	Unstable patients should have anaesthetic and/or critical care support.
GI bleeding was the cause of death in 36% and due to complications in 49%.	All deaths from major GI bleeds within 30 days of admission should undergo combined multidisciplinary peer review to identify remediable factors in patient care.
8% should have had escalation to critical care but did not	
64% of patients with AUGIB did not have any risk assessment score calculated.	GI bleed specialists need to develop risk stratification methods relevant to all GI bleeding.
6% should have had an interventional radiology procedure but did not.	Patients with any AUGIB should only be admitted to hospitals with 24/7 access to on-site endoscopy, interventional radiology (on-site or covered by a formal network), on-site GI bleed surgery, on-site critical care and anaesthesia.
32% of hospitals to which AUGIB patients are admitted do not have a 24/7 endoscopy service.	
73% of hospitals could not provide 24/7 embolisation of GI bleeding on-site. 45% had a formal network to combat this.	
51% of hospitals had formal network arrangements for TIPSS.	
35% of patients waited longer than 24 hours for an OGD.	All patients who present with major AUGIB should be discussed with the duty consultant responsible for major GI bleeds, within one hour of the diagnosis of a major bleed.
In 16% of cases the reviewers felt that the first consultant review was not sufficiently prompt for the patient's condition.	The ongoing management of care for patients with a major bleed should rest with, and be directed by the named consultant responsible for GI bleeds; to ensure timely investigation and treatment.
	All patients with a GI bleed and haemodynamic instability should have 24/7 access to an OGD within two hours of optimal resuscitation.
Important basic investigations were omitted in 20% admitted with AUGIB and 33% of inpatients.	The NICE Clinical Guideline (CG141) for AUGIB should be adhered to.
Of the 18% of patients who had complications, these could have been avoided with improved care.	
25% of hospitals to which patients with a GI bleed were admitted were not JAG accredited.	All hospitals which admit patients AUGIB should have their endoscopy units accredited by JAG
bleeding. Units that do not offer a TIPSS service should identify a specialist centre which offers a 24 h emergency TIPSS service and have appropriate arrangements for safe transfer of patients in place. <sup>18</sup>	<p><i>Follow-up</i></p> <p>All patients with cirrhosis should receive hepatology follow-up after discharge. This includes hepatocellular carcinoma surveillance (6-monthly <math>\alpha</math>-fetoprotein and ultrasound assessment), monitoring and managing liver disease and its complications, consideration of transplant assessment, and addressing variceal surveillance.</p>

## Discussion

Despite advances in endoscopic and medical therapy of AUGIB, outcomes following AUGIB remain poor. From the 2015 NCEPOD report, only 44.1% of patients were deemed to have received a good standard of care.<sup>2</sup> The most common deficiencies were in clinical care, with 45% of cases identified as having room for improvement.<sup>2</sup> Organisational factors were cited as requiring improvement in 18.5% of cases.<sup>2</sup> The key findings and recommendations from the report are outlined in Table 4. One of the main recommendations of the NCEPOD report is that the division of gastrointestinal bleeding into upper and lower is artificial and misleading, calling for NICE and SIGN to develop a combined gastrointestinal bleeding guideline.

It is worthwhile emphasising that mortality is often due to medical comorbidity, rather than uncontrolled bleeding.<sup>5</sup> With an increasing and ageing population, and

increased antithrombotic use, the burden of AUGIB is set to rise. Although AUGIB is managed endoscopically by gastroenterologists, approximately half of patients will remain under the care of the acute general physician.<sup>2</sup> Moreover, 14% develop AUGIB while admitted for a different condition, with significantly poorer outcomes.<sup>5</sup> As such, general physicians will continue to have a crucial role in the management of AUGIB. Streamlining of the general (internal) medicine-gastroenterology interface, adherence to evidence-based practice, and ensuring robust quality assurance of AUGIB management, are crucial for optimising patient outcomes. We hope that this review, covering peri-endoscopic management strategies in AUGIB, offers practical guidance for physicians and will lead to improved patient care. ①

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